THE EFFECT OF STYRENE EXPOSURE

ON THE

HUMAN NERVOUS SYSTEM

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SUMMARY

The purpose of this report is to provide a critical review of the literature pertaining to the acute and chronic effects of styrene on the human nervous system. Three research approaches to determining the effects have been assessed: psychological testing, neurophysiological testing, and worker symptom surveys. Each is reviewed in a separate section of this paper.

The neurophysiological testing and worker symptom surveys have proved to have little utility in assessing the effects of styrene on the human nervous system. The behavioural testing that has been reported falls into two categories: acute laboratory exposure studies and field studies involving chronically exposed workers. The acute exposure studies indicate that the acute effects of styrene (e.g. slowed reaction time) first occur or become detectable at a concentration between 100 ppm and 200 ppm.

The behavioural testing of chronically exposed workers involved reaction time studies and "paper and pencil" tests. The reaction time studies failed to produce any concrete evidence of impairment due to chronic styrene exposure. The results of the "paper and pencil" tests suggest that no chronic effects can be detected in workers chronically exposed to less than 100 ppm of styrene.

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INTRODUCTION

The psychological and neurophysiological effects of styrene have been under investigation during the last ten years. Unfortunately, the studies reported in the literature do not provide any clear-cut evidence as to what levels of exposure lead to chronic or acute nervous system effects. It is the purpose of this report to review and critique the literature and to provide, based on the evidence available, best estimates of the exposure levels at which styrene has acute and chronic effects on the human nervous system.

The approaches which have been adopted in determining the effects of styrene on the human nervous system fall into three categories: psychological tests, neurophysiological tests and symptom questionnaires. Each of these categories is dealt with in a separate section of this report. The psychological tests that have been employed include simple reaction time tasks and various paper and pencil tests. This category of investigations is examined in the first section of this report. The second category, neurophysiological tests, is dealt with in the second section which reviews studies that have employed electroencephalography and nerve conduction techniques. The third section critiques the studies which have relied upon worker self-reports of symptoms. The fourth and final section attempts an integration of the various findings in order to provide a best estimate of the exposure levels at which styrene has acute and chronic effects on the nervous system.

PSYCHOLOGICAL TESTS

Acute Exposure

Three studies have investigated the effects of acute styrene exposure on previously unexposed subjects. Stewart, Dodd, Baretta and Schaffer (1968) exposed subjects to styrene vapour concentrations of 50, 100, 200 and 375 ppm for periods ranging from one to seven hours. Six subjects exposed to 100 ppm of styrene for seven hours showed no impairment on tests of co-ordination and manual dexterity or on a modified Romberg test. Five subjects were exposed to an average styrene concentration of 376 ppm for one hour. Decrements in performance of the co-ordination and manual dexterity tests and the Romberg test were found although whether or not they were statistically significant was not reported. It is also unknown whether the decrements in the test scores represents an actual impairment in psychomotor performance or are due to reduced motivation due to the unpleasant symptoms reported by the subjects (e.g. nausea, headache etc.).

A very well controlled, single blind study by Gamberale and Hultengren (1974) exposed 12 subjects to four levels of styrene (50, 150, 250 and 350 ppm). The subjects acted as their own controls on five tests: number cancellation, Spokes test (join-the-dots), simple reaction time, three-choice reaction time, and a wire spiral test (a test of manual dexterity). Significant performance differences were found only in the reaction time test scores when the subjects were exposed to 350 ppm of styrene. There is, however, some question as to whether the subjects had reached equilibrium at the four styrene concentrations when they were tested since the styrene concentration in arterial blood samples had failed to reach a plateau during each of the exposures. The subjects were sequentially exposed to

the four styrene concentrations in one session moving to progressively higher levels at half hour intervals. Thus, it may be reasonable to assume that the subjects' performance decrement was observed when their styrene intoxication was close to a blood styrene concentration representing an exposure of at least 200 ppm.

It has been indicated by Lindstrom, Harkonen and Hernberg (1976) that a laboratory study (Oltramare, Desbaumes, Imhoff and Michiels, 1974) found a prolongation in simple reaction time after exposure to 50 ppm and in complex reaction time after exposure to 100 ppm of styrene. Such a finding, in addition to contradicting those of Gamberale and Hultengren (1974), lacks credibility from a theoretical standpoint. It is generally held (see Welford, 1968) that simple reaction time is a unitary component of complex reaction times. Given this, it is difficult to postulate a mechanism, other than learning effects in a multiple session experiment, to explain why complex reaction time was not found to be affected at the same styrene exposure level as simple reaction time.

Chronic Exposure

A number of studies have investigated the effects of styrene on individuals who were chronically exposed through their employment. The mean time-weighted exposure of the various groups tested have ranged from 8 ppm (Kjellberg, Wigaeus, Engstrom, Astrand & Ljungquist, 1979) to levels in excess of 150 ppm (Cherry, Waldron, Wells, Wilkinson, Wilson & Jones, 1980). Most of these studies employed reaction time tasks but some of them also employed various "paper and pencil" tasks. The findings of these latter tasks will be dealt with first.

(i) "Paper and Pencil" tests

In a study by Lindstrom, Harkonen and Hernberg (1976), seven different paper and pencil tests were administered to a group of 98 styrene-exposed workers, and 43 unexposed controls. Although the median styrene exposure was not stated in the paper by Lindstrom et al. (1978), Harkonen et al. (1978) have used urinary mandelic acid concentration in estimating the mean styrene exposure of the subjects to be approximately 36 ppm. The seven tests employed provided 29 measures of performance. On each of the measures a t-test was applied, without correction for multiple use, to compare the performance of the styrene-exposed workers with that of the controls. Only two measures achieved significance ($p<.05$): the number of reversals on the symmetry drawing test and the response latency on the Rorschach Inkblot Test. However, one of the t-tests would be expected to be a false positive by chance alone. Also, other test scores failed to show any differences between the groups, yet measured the same performance dimensions as the two which did. The pattern of results yield no evidence of any performance difference between the groups.

Dropping 43 exposed subjects from consideration Lindstrom et al. (1976) went on to compare the performance of 36 styrene exposed subjects whose urinary mandelic acid concentration indicated exposures below 25 ppm with the performance of 19 subjects whose imputed styrene exposure was greater than 75 ppm. Again, 29 t-tests were performed without correction for multiple testing. Two scores from the Mira test, one score from the Bourdon-Wiersma test and the score from the Symmetry Drawing test were found to indicate performance decrements in the high-exposure group. One Rorschach score was found to indicate significantly <u>superior</u> performance in the higher exposure groups. Once again it is difficult to see any coherent pattern of results suggesting an impairment

of any specific psychomotor performance. For example, the Mira form 1 score was found to reveal a performance difference between the two groups but the Mira form 2 score, although measuring exactly the same performance on a different form of the test, revealed no difference between the groups. Similarly, the high exposure group was found to have significantly poorer accuracy on the Bourdon-Wiersma Test but no performance decrement was found on the Wechsler digit-symbol substitution test; both tests are similar in the functional demands that they make.

Multivariate techniques were also employed to link the 29 test scores of the exposed subjects to the duration or intensity of their styrene exposures. Some weak relationships were found but the pattern of performance decrements were not related to other dependent variables measuring similar functions. Thus, these analyses are as unconvincing as the univariate analyses. For example, with the effect of age accounted for, two scores of the Kuhnberg Figure Matching test were found to have a significant ($p<.05$) joint partial correlation with the duration of styrene exposure. The two scores are held to be measures of visual memory and visomotor speed. It is difficult to understand why other test scores which measure much the same functions (e.g. simple reaction time, and the Wechsler logical memory scale) were not also found to be predictors.

An alternate analysis of the test results reported by Lindstrom et al. (1976) was performed by Harknonen, Lindstrom, Sepalainen, Asp and Hernberg (1978). The analysis was based upon defining cut-off values greater than the mean + 1 standard deviation of the reference group's scores as representing abnormal performance. Based on these cut-off values, styrene exposure ranges at which performance levels became abnormal were determined. As in the earlier analyses the findings are not convincing. Only three scores

(one from each of the Mira, Symmetry Drawing and the Bourdon-Wiersma) out of a possible 29 were employed in the analyses, once again indicating an absence of a coherent pattern of findings.

Kjellberg et al. (1979) studied seven workers employed in a boat plant (who were exposed to both styrene and acetone) and seven matched controls. The TWA exposures of the subjects exposed to styrene was between three and 14 ppm. Three tests were employed by Kjellberg et al. (1979): the Bourdon-Wiersma test, a mental addition task, and a simple reaction time task. The findings of the reaction time task will be discussed later in this paper. The tests were administered to the subjects once in the morning before work and once after work; the time of first testing was counter-balanced. The Bourdon-Wiersma test revealed no performance differences between the exposed and control groups in either speed or accuracy. Similarly, no difference was found between groups in the speed and accuracy on the mental arithmetic task. Both tests were found to be sensitive to learning effects. The authors indicated that the results of the tests cannot be attributed directly to the styrene exposure because of the presence of the acetone in the work environment. Their point is well taken and it should be remembered that in other styrene studies employing industrial workers acetone exposure is more than likely a concomitant of styrene exposure because of acetone's use as a solvent in many of the processes involving styrene.

Cherry, Waldron, Wells, Wilkinson and Jones (1980) tested 27 boat plant workers exposed to styrene and 27 workers from the same plant who were not exposed. The two groups were similar in age and education. The subjects were tested on Monday mornings before work so that the exposed group's styrene burden would be minimal. The tests were repeated after the day's work. The mean TWA exposure of the exposed

group was 92 ± 46 ppm with the afternoon exposure being lower (52 ± 35 ppm) than the morning exposure (117 ± 63 ppm). Four performance tests were employed:

(1) number cancellation (similar to the Bourdon-Wiersma test);
(2) digit-symbol substitution test;
(3) digit span, forward and backward and
(4) one minute tapping speed.

No significant performance differences were found between the exposed and control groups in the morning tests. Similarly, no significant difference was found between the two groups when the performance change from the the morning to afternoon tests were compared. This study appears to have been reasonably well controlled. The subjects were practiced (although not to asymtotic performance) on the Friday prior to the Monday test thus giving some control over learning effects. Time of day effects were also controlled by testing all of the subjects in small groups between the same hours on five successive weeks.

A study by Mutti, Mazzucchi, Frigeri, Falzoi, Arfini and Franchini (1983) employed a variety of tests in comparing 50 styrene-exposed workers (exposures ranged from 10 ppm to 300 ppm) with 16 controls. Four of the tests were drawn from the Wechsler Adult Intelligence Scale test: vocabulary, logic memory (immediate and delayed recall of story elements), digit symbol substitution and block design. In addition, an embedded figures test and a ten item word list, used to test immediate and delayed recall from long-term memory, were also administered. It was found that the performance of the exposed workers was significantly poorer on three of the four memory tests. Only the delayed recall of the word list was not significantly different between the two groups. The digit-symbol substitution test also revealed

no significant difference in performance. The performance of the exposed workers was also significantly poorer on the block design and embedded figures tests. Interpretation of these results is difficult because it is not clear that the two groups are comparable. The mean age of the exposed workers was 5 years greater than that of the controls. In addition, the controls had a superior mean score on the vocabulary test which the authors held to be a measure of general intelligence. Thus, it may be seen that the performance differences observed between the groups could be due to the younger age and superior general intelligence of the control subjects or due to the styrene to which the workers had been exposed.

Partial correlations between the various test scores (corrected for age and vocabulary score) and the duration of the styrene exposures were calculated. Only the digit-symbol substitution score was significantly correlated with exposure duration. Partial correlations between corrected test scores and an index of current exposure (sum of urinary mandelic acid and phenylglyoxylic acid concentrations) were also calculated. Only block design test scores were significantly correlated with the current exposure index.

It is apparent that the findings of this study do not present any coherent pattern of impairment that can be attributed directly to styrene exposure.

(ii) Reaction time tests

Five studies have employed various reaction time tasks in assessing psychomotor performance effects in workers with chronic exposure to styrene. Gotell, Axelson and Lindelof (1972) measured simple reaction time in styrene-exposed workers and 17 age-matched controls. The reaction time test was administered mid-week before and after work. When

compared to the control group the styrene-exposed workers had significantly longer reaction times in the morning test but not in the afternoon test. The exposed group was divided into two subgroups. Subgroup one contained 11 workers whose TWA styrene exposure was less than 150 ppm (range: 17-139 ppm). Subgroup two contained six workers whose TWA styrene exposure was above 150 ppm (range: 235-292 ppm). The reaction time performance of the first subgroup did not differ from that of their age-matched controls on either the morning or afternoon test. The more highly exposed group's performance was significantly ($p<.05$) worse than the control group's performance on both the morning and afternoon tests. Although the results appear fairly clear-cut, it must be stated that the reaction time apparatus and the method of testing were extremely crude. The subjects were given only three practice trials and ten data trials in each of the two sessions. Thus, the data must be viewed as contaminated with learning effects and the measures themselves (i.e. mean reaction time for ten trials) as being possibly affected by one or two extremely long reaction times.

Cherry et al. (1980) measured the reaction times of 27 styrene-exposed shipyard workers with 27 matched controls at the same time as they administered the tests described previously in this paper. In the morning after a weekend away from styrene exposure the experimental group's mean reaction time was significantly ($p<.05$) longer than the control group's mean reaction time. At the end of the day (mean TWA exposure = 96±46 ppm) the control group's performance was still significantly ($p<.05$) better than that of the exposed group. However it was found that the control group's mean reaction time had increased by 5.5 ms over the day while the exposed group's mean reaction time had decreased by 9 ms. Like Gotell et al. (1972), Cherry et al. (1980) split their exposed group into high and low exposure

subgroups using a criterion of a blood styrene level of 5.5 µmol/l. This division allowed them to demonstrate that most of the exposed group's improvement in reaction time performance was attributable to 13 subjects with blood styrene levels below 5.5 µmol/l. This pattern of results indicates that individuals with low amounts of styrene in their blood had improved reaction time performance after a day's labour while the performances of unexposed individuals and individuals with high blood styrene levels remained virtually unchanged. This pattern of results is anomalous given styrene's known narcotic effects and could be due to some uncontrolled factors in the experiment such as the amount of physical work required by the various occupations in both the exposed and unexposed groups. It was pointed out by Cherry et al. (1980) that physical work can increase styrene uptake. By extension, it could be postulated that the unexposed group and the high exposure group had worked harder and were more fatigued than the low exposure group. Consequently it follows that fatigue may have been the causative factor in the findings and that blood styrene levels were merely an indirect measure of the fatigue. Some credibility is given to this argument by the fact that the high exposure group reported significantly ($p<.05$) larger increases in physical and mental tiredness over the course of the day than did the other two groups. Of course, styrene-exposure could be the direct or indirect (as in the case of reaction time) factor in this finding.

Some of the same investigators performed a follow-up study, and a re-analysis of the Cherry et al. (1980) data (Cherry, Rodgers, Venables, Waldron and Wells, 1981). In re-analyzing the data from the first study it was found that a significant ($p<.01$), positive correlation ($r = .75$) existed between the concentration of mandelic acid (a styrene metabolite) in the urine samples collected during the first three hours of the shift and the reaction time at the start

of the shift. Since the subjects had been unexposed to styrene for two days prior to being tested it is impossible to tell whether the mandelic acid concentrations reflect styrene exposure prior to the reaction time test or styrene exposure subsequent to the test or both subsequent and prior exposures. In the follow-up study the end of shift reaction time was significantly ($p<.05$), negatively correlated ($r= -0.69$) with urinary mandelic acid concentration. This finding came from 10 workers on their first day back at work after a two week holiday.

Taken as a whole the two studies by Cherry and his co-workers have failed to demonstrate any clear-cut psychomotor effects attributable to styrene exposures of approximately 100 ppm. The inability to demonstrate a clear effect due to a day's exposure indicates that the difference in performance between the exposed and control groups may not be due to styrene exposure but to some other factor or factors.

A very well controlled reaction time study was carried out by Gamberale, Lisper and Olson (1976). The study tested the performance of 106 styrene-exposed workers from four different shipyards and 36 unexposed workers from light manufacturing plants. The mean ages and ranges of the two groups were similar. The exact mean styrene exposure level of the shipyard workers was not determined but has been estimated to be approximately 50 ppm by a colleague of the principal investigator (see Kjellberg, Wigaeus, Engstrom, Astrand and Ljungquist, 1979). A simple visual reaction time task was employed and 160 trials over ten minutes (random inter-trial interval) constituted one session. Each subject was tested in two sessions, one in the morning before work and one in the afternoon after work. In order to control learning and time of day effects half of the subjects received their first session in the morning and

half received their first session in the afternoon. The authors also report attempting to control lighting conditions and the physical orientation of the apparatus with respect to the subject. These two factors can have significant impact on reaction time and this is the only study investigating the effects of styrene which has reported attending to these factors at all.

Two dependent measures were employed: mean reaction time for each session (am or pm) and the increase between the median reaction time in the first minute of testing and in the tenth minute of testing. In comparing the mean reaction times of the exposed and control groups, it was found that the exposed group was significantly slower in the morning ($p<.02$) and in the afternoon ($p<.001$) sessions. The exposed group's increase in median reaction time was significantly greater ($p<.02$) only in the afternoon (after work) test session. The performance of the exposed workers did not change between sessions. It was found that there was no significant difference on either test measure between the morning and afternoon sessions in the exposed group. In the control group however, mean reaction time was significantly ($p<.02$) better in the afternoon session. Also, the control group's median increase was significantly smaller ($p<.001$) in the afternoon session. The authors argue that this pattern of results suggests that in the morning the exposed workers were still suffering the effects of the previous day's exposure (or had undergone some permanent change) and that the day's exposure was sufficient to counteract the afternoon improvement observed in the control group.

In an attempt to further demonstrate the effects uncontaminated by the possible effects of age, each of the 36 control group workers was matched for age with two styrene-exposed workers, one from each of the two major employment categories (assemblers and fitters). The median

reaction time of the 10 one minute blocks of the subjects was analyzed in a three-way analysis of variance on the factors of group (3), time blocks (10) and test session (2, am/pm). The first two factors were found to be significant ($p<.001$) but the test session factor was found not to be significant. A significant interaction ($p<.05$) between groups and time blocks was also found. These results indicate that: (1) the exposed groups had longer reaction times than the controls (2) the performance of the three groups deteriorated over the ten minute sessions and the performance of the exposed workers deteriorated more than that of the controls (3) since there was no group by session interaction the performance differences between the exposed and control subjects were the same in the afternoon and morning sessions, i.e. the day's exposure to styrene had no effect on the exposed group's performance.

The first two outcomes of the analysis are in agreement with the overall analyses performed on the entire subject population's performance. The third outcome, suggesting that the performance differential between the exposed and control workers was unchanged between morning and afternoon sessions, is contrary to the findings of the overall analysis. Given that age is a significant factor in reaction time performance (Welford, 1958) and given that age is much more tightly controlled in the second analysis it must be concluded that the day's exposure to styrene had no effect on the performance of the exposed workers. All that can be concluded is that the exposed workers' reaction time performance was significantly poorer than the controls. Whether this observed difference can be directly attributed to styrene is indeterminate, i.e. there is no causal link between the impairment and the styrene exposure and other factors may be responsible.

A study by Lindstrom et al. (1976) tested the reaction times

of 98 styrene-exposed workers and 43 controls. The median TWA exposure level of the exposed workers was approximately 36 ppm. The subjects were tested for left-handed, right-handed and two handed responding. No difference in reaction time performance was found between the two groups and no relationship between reaction time performance and various indices of exposure were determined.

Kjelberg et al. (1979) have reported a study using reaction time apparatus and control methods employed previously by Gamberale et al. (1976). Only seven styrene-exposed (average TWA exposures - 8 ppm) and seven age-matched controls were tested. The primary dependent measures were the median reaction time of one minute time blocks (16 trials) and the 75th percentile of the ten blocks. Analysis of variance (groups, time block, session) revealed no significant main effects. A significant ($p<.05$) interaction between groups and session was found but it is difficult to accept as being meaningful given the small differences it represents and the absence of significant main effects. Taken as a whole this study has failed to demonstrate any meaningful effects because of too small a sample size and (probably) because no effects occur at such low levels of exposure.

A choice reaction time task was employed in a study by Mutti et al. (1983) in which the performance of 50 styrene-exposed workers (range: 10 ppm-300 ppm) and 16 controls was examined. Little information about the task methodology is given by the authors but it can be deduced from their paper that the results are based upon very few trials and that little or no practice was given to the subjects. The task itself consisted of three coloured stimulus lights and a tone stimulus; two of the lights and the tone required three different responses, the third light required no response. Mean reaction times were based upon the reaction times to

the two light stimuli. No reason was offered for dropping the set of response times to the tone.

The results of this test were quite dramatic; the mean reaction time of the 50 styrene-exposed subjects was 128.3 ms longer than that of 16 control subjects. This finding is somewhat surprising since Gamberale and Hultengren (1974) were only able to find a difference of 17 ms in the choice reaction time performance of subjects exposed to air and exposed to 350 ppm of styrene in a controlled laboratory experiment. When the reaction times were corrected for age and score on the vocabulary general intelligence test they were significantly correlated with both the exposure duration ($p<.05$) and current exposure level as measured by the urinary concentraton of styrene metabolites ($p<.01$). The effects observed in this study are considerably larger and more clear-cut than any of the other reaction time studies reviewed in this paper. In light of the apparent methodological shortcomings and the dropping of some data without explanation, it would be prudent to await some replication of these findings before basing any decisions upon them.

A study of the neurophysiological effects of styrene has been reported by Rosen, Haeger-Aronsen, Rehnstrom and Welinder (1978). In their study they examined three groups of workers exposed to 125 ppm, 44 ppm and less than 5 ppm of styrene. The subjects were also tested on ". . . a wide spectrum of tests covering intellectual as well as psychomotor functions". It was stated that the test results would be published separately but a computer search of a number of library databases suggests that it was not. It is possible that the results were never published due to a lack of significant findings.

It has been reported (NIOSH, 1983) that a study by Brooks,

Anderson, Buncher, Carson, Ella, Emmet and Tsay (1979) employed a choice reaction time task. Two groups of styrene-exposed workers were tested. One group of workers had a mean TWA exposure of about 9 ppm; the other group had a mean TWA exposure of 82 ppm. The two groups of workers were tested both before and after their work shifts, and no differences in their reaction time performance were found.

NEUROPHYSIOLOGICAL TESTS

Electroencephalography

Several studies have employed EEGs in attempting to detect changes in subjects exposed chronically to styrene. Seppalainen and Harkonen (1976) performed one such study on the same 96 styrene-exposed subjects that took part in the study by Lindstrom et al. (1976). Twenty-two of them had one of three types of abnormalities: localized slow activity (13 workers), diffuse theta activity (eight workers) and bilateral spike and wave discharges (one worker). Although the abnormalities were described as mild their frequency was significantly ($p<0.01$) higher than the 10% that the authors claimed to exist in the general population. It was also found that in subjects with urinary mandelic acid concentration below 700 mg/dm^3, the frequency of abnormal EEGs was the same as the general population, but in subjects with concentrations beyond that level the frequency rose to 33%. No evidence was found to suggest a dose-response relationship i.e. higher frequencies were not found among subjects with higher mandelic acid levels. No relationship was found between duration of exposure and frequency of EEG abnormalities. Similarly, in a later paper, Harkonen (1977) reported finding no relationship between symptoms reported by the subjects and the abnormal EEGs.

Another EEG study has been reported by Rosen et al. (1978). In this study 33 workers with varying degrees of styrene exposure were tested. It was found that 27% (9/33) of these workers had increased fast activity within central and frontocentral areas; 18% (6/33) had increased amounts of slow activity over both hemispheres. Four of the six subjects with slow activity had exposures to styrene less than 5 ppm while none of the 13 subjects exposed to 125 ppm displayed the abnormality.

Several other studies employing the EEG to detect styrene-induced changes have been reviewed elsewhere (NIOSH, 1983) and, as in the case of the two studies described above, no pattern of EEG abnormalities has been identified as being due to styrene exposure. Neither has any link been established between the degree of exposure or duration of exposure and EEG abnormalities.

EEG recordings are subject to considerable variation within any given individual (Hawkes and Prescott, 1973) and are also subject to modification by a variety of factors (Petersdorf, Adams, Braunwald, Isselbacher, Martin and Wilson, 1982). Given this, and the absence of any consistent pattern of EEG findings and the absence of any association of EEG abnormalities with other evidence of styrene-induced changes, the preceding studies are best viewed as providing only a very weak suggestion of styrene-induced nervous system changes.

Nerve Conduction Studies

Nerve conduction studies were carried out by Rosen et al. (1978). Thirty-three workers with ages ranging from 23 to 65 years, exposed to various levels of styrene (5-125 ppm) for varying lengths of time (1-21 years) were tested along with six controls aged 22 to 57 years. The motor conduction velocities of the exposed workers were not different from those of the controls. It was also found that some sensory nerve parameters showed significant impairments in the styrene-exposed group relative to the control group.

Ten exposed subjects were classified, based on their neurographic results, as having "possible sensory neuropathy". The factors that differentiated this group from the remaining 23 exposed subjects was age ($p<.0005$) years of exposure ($p<.025$) and a measure expressing both

duration and severity of exposure ($p<.01$). It is obvious, however, that the latter two factors would be highly correlated with age and that consequently the observed possible neuropathies are probably due to age rather than styrene exposure.
Another study (Lilis, Lorimer, Diamond & Selikoff, 1978), also tested the nerve conductions of styrene exposed workers. Low radial nerve conduction velocities were found in 18.8% of the workers tested. Low peroneal nerve conduction velocities were found in 16.4% of the workers tested. No statistically significant relationships were found between the conduction velocities and the factors of length of styrene exposure and age.

Seppalainen and Harkonen (1976) tested the nerve conduction velocities of 40 styrene-exposed workers. As a group the workers did not differ from a group of age-matched control subjects. Nine of the exposed workers were found to have one or more abnormal conduction velocities. Five of the nine subjects' abnormalities could be attributed to causes other than styrene exposure. The remaining four had low styrene exposures and the authors claimed that no connection between styrene exposure and neuropathy could be made.

It appears from the preceding studies that there is little evidence to link styrene exposure with peripheral nervous system effects.

SYMPTOM SURVEYS

A number of studies have investigated the symptoms and subjective evaluations reported by workers chronically exposed to styrene. In a study of 494 workers, Lorimer, Lilis, Nicholson, Anderson, Fischbein, Daum, Rom, Rice and Selikoff (1976) administered a symptom questionnaire. It was found that significantly ($p<.01$) more of the workers judged to have high exposures had experienced acute pre-narcotic symptoms (e.g. headache, dizziness etc.).

Harkonen (1977), investigating the same 98 workers as Lindstrom et al. (1976) and employing a control group of 98 unexposed workers administered a symptom questionnaire. The questionnaire covered general symptoms and symptoms related to acute styrene exposure. The questionnaire revealed that the styrene-exposed (median TWA exposure 30 ppm) workers reported symptoms of fatigue, concentration difficulties, and symptoms of irritation significantly more often ($p<.01$) than their controls. During the workday pre-narcotic symptoms were also reported significantly more often ($p<.001$) by the exposed workers. No relationships of symptoms or symptom scores with exposure levels, abnormal EEGs, or low psychological test scores were found. In another paper, Lindstrom, Harkonen and Mantere (1978) examined the alcohol consumption and tolerance of the 98 styrene-exposed workers and their controls. It was found that styrene-exposure was not related to any aspect of alcohol consumption.

Gamberale et al. (1976) administered a 32 item questionnaire to 106 styrene-exposed (approximately 50 ppm) and 36 unexposed workers before and after a shift. The questionnaire was designed to assess the workers' emotional states. No significant differences were found between the two groups or between the two test sessions.

Rosen et al. (1978) reported the symptoms of 33 styrene exposed workers and six controls. The exposed subjects were divided into three groups (10, 10 and 13) based upon their exposure to styrene. The mean exposure levels for the three groups were 5, 47 and 125 ppm, respectively. The percentage of each group reporting various pre-narcotic symptoms was presented. The differences between the groups were not statistically significant but it appears that some weak association between symptom reporting and the level of exposure may have existed amongst these subjects.

Cherry et al. (1980) employed a questionnaire designed to determine the subjects feelings of physical and mental tiredness, sleepiness and general health. Twenty-seven styrene-exposed workers and their age-matched controls filled out the questionnaire before and after their shifts. In the morning (before shift), no differences in responding between the two groups were detected. In the "after work" questionnaire it was found that significant score changes from the morning questionnaire existed between the 27 controls, 13 low-exposure subjects (blood styrene <5.4 µmol/l) and 14 high exposure subjects on the dimensions of: physical tiredness ($p<.01$), mental tiredness ($p<.05$) and general health ($p<0.01$). In each case it was the high exposure subjects that had undergone the largest change. When the two exposed groups were combined only "general health" was found to have deteriorated significantly ($p<.05$). Similarly, a discriminant analysis revealed that only the change in score for general health contributed to discrimination between the three groups. When the low styrene exposure group and the control group were combined and compared with the high exposure group in another discriminant analysis it was found that discrimination between the groups could be achieved using the change scores of sleepiness, physical tiredness and general health. The interpretation of these findings is difficult since none of

the psychological tests revealed any significant differences between the groups which might have been expected given the increased tiredness, sleepiness and deterioration in general health. Cherry et al. (1980) indicated that the results of the questionnaires could have been biased by the workers' prior knowledge of the purpose of the study.

Other studies, reviewed elsewhere (NIOSH, 1983), have found patterns of responses similar to those reported in the preceding studies. Unfortunately no evidence linking subjective reports to any quantifiable impairment has been found and, given the inherent reporting bias problem of survey techniques, no such evidence is likely to emerge.

SUMMARY OF FINDINGS

It is apparent from the preceding sections that no clear-cut evidence exists indicating the level of chronic exposure to styrene that results in any psychological or neurophysiological effects. The EEG studies (e.g. Rosen et al., 1978) presented some weak evidence that styrene may have some link to the presence of abnormal EEGs. It must be remembered, however, that little similarity in the kinds of abnormalities found exists between the studies. Also, no relationships between abnormal EEGs and the intensity or duration of the exposure have been determined nor has any relationship been established between the abnormal EEGs and psychological test results or the presence or absence of symptoms. The nerve conduction studies (e.g. Seppalainen and Harkonen, 1976) were similarly unable to link any finding to the various aspects of styrene exposure.

Symptom surveys, due to inherent problems of bias, have little concrete information to offer except to confirm the fact that individuals working with styrene do occasionally experience pre-narcotic symptoms. The levels at which this happens are unknown but it seems likely that some of the experiences would be the consequence of short, high exposures.

Three studies have addressed the effects of acute styrene exposure. Stewart et al. (1968) demonstrated no effects on coordination or manual dexterity with a seven hour exposure to 100 ppm of styrene. The same study presented some evidence of coordination and dexterity impairment with a one hour exposure to 376 ppm of styrene. Oltramare et al (1974) have apparently presented some theoretically inconsistent simple reaction time and choice reaction time evidence suggesting that the effect of styrene on psychomotor performance may start at levels as low as 50 ppm. In

clearly the best controlled study Gamberale and Haltengren (1974) found reaction time performance impairment but no coordination or dexterity impairments at a styrene exposure level of approximately 200 ppm. Below this level no effects were found. Taken as a whole these findings suggest that acute psychomotor effects of styrene may become detectable at exposure levels between 100 ppm and 200 ppm.

The psychomotor and cognitive effects of chronic exposure to styrene and the level at which they occur are considerably more difficult to demonstrate. Paper and pencil tests (e.g. the Bourdon-Wiersma test) have been administered to groups of subjects with mean exposure levels ranging from 8 ppm to 92 ppm. Kjellberg et al. (1979) found no performance differences between exposed workers' (8 ppm) and their controls. Cherry et al. (1980) had similar findings with workers who had a mean exposure of 92 ppm. Only Lindstrom et al. (1976) found any statistically significant differences when they compared exposed (median exposure of approximately 36 ppm) workers scores on some aspects of some tests, with those of control workers. The lack of a coherent pattern of results suggests that the differences were probably statistical artifacts. Taken together, these findings suggest that with chronic exposure levels below approximately 100 ppm any chronic psychological impairments are either non-existent or too subtle to be detected by the tests. Both the Kjellberg et al. (1979) and Cherry et al. (1980) studies tested subjects prior to, and after, a day's exposure and found no differences in psychological performance thus providing some confirmation of the no effect level (100 ppm) derived from the laboratory studies.

Several studies have employed reaction time tasks to determine the chronic styrene exposure levels which lead to deterioration of psychomotor performance. Gotell et al. (1972) were able to demonstrate that six workers with TWA

exposures greater than 150 ppm had significantly worse performance than their age-matched unexposed controls both before starting work and after work. It was not demonstrated that the after-work, post-exposure performance was significantly poorer than the pre-work performance. Thus there is no proof that the day's styrene exposure had any effect on performance. Without demonstrating this effect there is no good reason to assume that the observed differences between the groups are attributable to styrene at all - a myriad of alternate explanations can be advanced, from subject anxiety to poor experimental control. Cherry et al. (1980) presented a similar pattern of results with workers exposed to a mean TWA concentration of 92 ppm. Gamerale et al. (1976) also found the same pattern of results in workers with a mean TWA exposure of approximately 50 ppm. Findings indicating no pattern of reaction time performance deficits have been reported by Lindstrom et al. (1976) (36 ppm) and Kjellberg et al. (1979) (8 ppm).

Since the reaction time studies can offer no substantial proof of chronic styrene-induced psychomotor impairment, the only information available pertaining to chronic psychomotor impairment are the results of "paper and pencil tests". The results of these tests, administered to chronically exposed workers, suggest that there are no effects below approximately 100 ppm.

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